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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Ning Man Cheng

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EXAMINER

CHOWDHURY, IQBAL HOSSAIN

ART UNIT

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1652

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/518,223	<b>Applicant(s)</b> CHENG ET AL.	
	<b>Examiner</b> IQBAL H. CHOWDHURY	<b>Art Unit</b> 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 28 and 43-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 47-56 is/are allowed.
- 6) ☒ Claim(s) 28 and 43-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Claims 28, 43-46 and 47-56 are currently pending.

In response to a previous Office action, a non-final action (mailed on September 18, 2008), Applicants filed a response and amendment on December 18, 2008, amending claim 43, canceling claims 24, 27, 38-39 and 42, and adding new claims 47-56 is acknowledged.

Claims 28, 43-46 and 47-56 under consideration and are present for examination.

Applicants' arguments filed on December 18, 2008, have been fully considered and are deemed persuasive to overcome the rejections as previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Nevertheless, upon reconsideration, the rejection under 103 is re-instated on a different basis which is designated as a new ground of rejection.

### ***New-Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28 and 43-44 are rejected under 35 U.S.C. 103 (a) as being obvious over Vockley et al. (Arginase II, US 6316,199 B1, issue date 11/13/2001, see IDS) and Clark et al. (WO 02/44360, publication 6/6/2002, see IDS) in view of Mehvar et al. (Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation, J Pharm Pharmaceut Sci, 3(1):125-136, 2000, see PTO-892).

Instant claims are directed to a method of treating human liver, breast, colon or rectal malignancies comprising administering to a subject a modified, full-length recombinant human arginase I polypeptide, which is covalently linked to polyethylene glycol (PEG), wherein administration of modified full-length recombinant arginase I polypeptide reduces physiological arginine level in the subject to below 10  $\mu$ M for at least 3 days.

Vockley et al. teach human arginase II and I, which degrades arginine to ornithine and urea, resulting in reducing the arginine level, and a method for treating human cancer including prostate cancer by administering arginase II polypeptide (see Col 3, line 37-38). Vockley et al. also teach recombinant expression of human arginase II, expression in Sf9, Cos and *E. coli* followed by purification by affinity chromatography

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due to the presence of HA tag (Example 3 and 4), which results substantially purified protein (see Col 11, line 55-66). Vockley et al. further teach a pharmaceutical composition comprising human arginase II for treating said cancer (see Col 3, line 13-17) and pegylated said protein by treating with polyethylene glycol (PEG) to increase the half-life of the protein in serum and reduce the antigenicity to be an effective therapeutic composition for treating cancer (see Col 14, line 47-64). The arginase II gene was found using probes based on arginase I which was shown to have considerable sequence homology.

Vockley et al. does not disclose the composition comprises arginase I or the use of arginase I for treating liver, breast, colon, and rectal malignancies. Vockley et al. do not teach reducing arginine level below 10 $\mu$ M for at least 3 days and increase the half life of the pegylated arginase to 21 days.

Clark et al. teach modified arginine deiminase, an arginine degrading enzyme, which is modified with polyethylene glycol (PEG) and a method of treating cancer including sarcomas, hepatomas (a liver cancer) and melanomas (page 2, line 28-31, page 3, line 1-3). Clark et al. do not teach reducing arginine level below 10  $\mu$ M for at least 3-21 days by increasing half-life of pegylated arginase I.

Mehvar et al. teach the half-life of arginase protein of 12 hrs after pegylation with polyethylene glycol and further teach that said arginase conjugate increased the survival time in mice with Taper liver tumor (page 128, left column, line 3-8).

Vockley et al. indeed teach arginase I and a method of treating cancer with arginase II, an isoform of arginase I having identical function of degrading arginine,

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wherein said arginase II is modified with PEG, which increased the half life arginase, which can be used for treating cancer including prostate cancer. Clark et al. provide additional motivation for using arginine degrading enzyme for treating hepatomas, a liver cancer. Mehvar et al. teach treating mice with arginase protein (without specifying if it is arginase I or arginase II) modified with PEG, which increased the half-life of the pegylated arginase in mice to 12 hrs in a treatment of Taper liver tumor.

Therefore, combining the teachings of Vockley et al. Clark et al. and Mehvar et al. it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace arginase II with arginase I as taught by Vockley et al. and use the method of Vockley et al. to make a therapeutic composition comprising human arginase I pegylated with PEG as taught by Vockley et al. Clark et al. and Mehvar et al. for treating cancer including liver cancer as taught by Clark et al. and administering said pegylated arginase in a patient and monitoring the half-life of the pegylated arginase in the serum for 3-21 days as Mehvar et al. clearly indicated that pegylated arginase half-life can be increased to 12 hrs. The substitution of arginase II by arginase I is obvious because the two enzymes have identical activity. See KSR Int'l Co. V. Teleflex, Inc. 82 USPQ2d 1385 (2007).

One of ordinary skill in the art would have been motivated to replace arginase II by arginase I in view of its identical activity to arginase II, which has been shown to use in treating cancer by reducing the arginine level because arginine is regarded as the cancer-related chemical *in vivo*. One of ordinary skill in the art would have been motivated also to use pegylated arginase to increase the half-life of the enzyme for at

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least 3-21 days in serum to increase the effectiveness of the enzyme against malignant cell in order to treat cancer, since, Vockley et al. and Mehvar et al. clearly teach the increased half life of arginase protein by pegylation, which is effective for the treatment and one ordinary skill in the art would be able to increase the half life of pegylated arginase I to 3-21 days by optimizing the pegylation of arginase I by using high molecular weight PEG and monitoring arginase and arginine concentration in the serum, which is a matter of routine experimentation and obvious to one of skilled artisan to obtain better results.

One of ordinary skill in the art would have a reasonable expectation of success because Vockley et al. could successfully used arginase II, which is an isoform of arginase I having identical function, i.e. arginine degrading activity for treating cancer.

Therefore, claims 28 and 43-44 would have been *prima facie* obvious to one of ordinary skill in the art.

### **Conclusion**

#### **Status of the claims:**

Claims 28, 43-46 and 47-56 are pending.

Claims 28 and 43-46 are rejected.

Claims 47-56 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Iqbal Chowdhury, PhD, Patent Examiner

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/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657